

# Routine antenatal anti-D prophylaxis for women who are rhesus D negative

Technology appraisal guidance

Published: 27 August 2008

[www.nice.org.uk/guidance/ta156](https://www.nice.org.uk/guidance/ta156)

## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

# Contents

1 Guidance.....	4
2 Clinical need and practice .....	5
3 The technologies.....	8
4 Evidence and interpretation.....	10
4.1 Clinical effectiveness .....	10
4.2 Cost effectiveness.....	12
4.3 Consideration of the evidence .....	15
5 Implementation .....	19
6 Recommendations for further research .....	20
7 Related NICE guidance .....	21
8 Review of guidance.....	22
Appendix A: Appraisal Committee members, guideline representatives and NICE project team.....	23
A Appraisal Committee members .....	23
B Guideline representatives .....	25
C NICE project team .....	26
Appendix B: Sources of evidence considered by the Committee .....	27
Changes after publication .....	29
About this guidance .....	30

This guidance replaces TA41.

# 1 Guidance

This guidance replaces 'The clinical effectiveness and cost effectiveness of routine anti-D prophylaxis for RhD-negative women in pregnancy' (NICE technology appraisal guidance 41) issued in May 2002.

For details, see '[About this guidance](#)'.

- 1.1 Routine antenatal anti-D prophylaxis (RAADP) is recommended as a treatment option for all pregnant women who are rhesus D (RhD) negative and who are not known to be sensitised to the RhD antigen.
- 1.2 When a decision has been made to give RAADP, the preparation with the lowest associated cost should be used. This cost should take into account the lowest acquisition cost available locally and costs associated with administration.

## 2 Clinical need and practice

- 2.1 Human red blood cells carry many antigens on their surfaces. The most important of these antigens belong to the ABO system and the rhesus (Rh) system. The D antigen is the most important antigen of the rhesus system. People with the rhesus D (RhD) antigen are referred to as RhD positive, and those without it as RhD negative. A baby inherits its blood type from both parents. Therefore a mother who is RhD negative can carry a baby who is RhD positive. During pregnancy small amounts of fetal blood can enter the maternal circulation (an event called feto–maternal haemorrhage or FMH). The presence of fetal RhD-positive cells in her circulation can cause a mother who is RhD negative to mount an immune response, producing a template for the production of antibodies as well as small amounts of antibodies against the RhD antigen (anti-D antibodies). This process is called sensitisation or alloimmunisation.
- 2.2 Sensitisation can happen at any time during pregnancy, but is most common in the third trimester and during childbirth. Sensitisation can follow events in pregnancy known to be associated with FMH, such as medical interventions (chorionic villus sampling, amniocentesis or external cephalic version), terminations, late miscarriages, antepartum haemorrhage and abdominal trauma. It can also occur in the absence of an observed potentially sensitising event. The risk of sensitisation is affected by the ABO blood type of the fetus, with a lower risk if it is incompatible with the mother's ABO type. Sensitisation depends on the volume of fetal blood entering the mother's circulation and the magnitude of the mother's immune response. The risk of sensitisation is greatest in the first pregnancy and decreases with each subsequent pregnancy. Once sensitisation has occurred it is irreversible.
- 2.3 The process of sensitisation has no adverse health effects for the mother and usually does not affect the pregnancy during which it occurs. However, if the mother is exposed to the RhD antigen during a subsequent pregnancy, the immune response is quicker and much greater. The anti-D antibodies produced by the mother can cross the placenta and bind to RhD antigen on the surface of fetal red blood cells.

These antibody-coated fetal red blood cells are removed from the fetal circulation. Fetal anaemia results if the red blood cells are removed faster than they are produced. Severe anaemia can lead to fetal heart failure, fluid retention and swelling (hydrops), and intrauterine death. Before birth, anaemia and hydrops can be managed with intrauterine transfusions, but this carries a 2% risk of fetal loss. When red blood cells are broken down, bilirubin is released. In utero this is cleared by the placenta and is not harmful. However, after birth the neonatal liver cannot cope with the excess production of bilirubin, and this leads to jaundice (haemolytic disease of the newborn or HDN). Low levels of jaundice are not harmful but, if left untreated, higher levels can result in damage to specific areas of the neonatal brain, causing permanent brain damage (kernicterus). This can lead to a range of neurodevelopmental problems, such as cerebral palsy, deafness, and motor and speech delay. Postnatal jaundice can be treated with phototherapy and exchange transfusion.

- 2.4 The risk of sensitisation can be reduced by administering anti-D immunoglobulin to women in situations in which FMH is likely (after delivery, miscarriage, abortion, invasive procedures or abdominal trauma). Potentially sensitising events introduce a quantity of fetal RhD antigen into the maternal circulation. The anti-D immunoglobulin administered neutralises this fetal antigen. In addition, anti-D immunoglobulin can be administered routinely in the third trimester as prophylaxis against small amounts of FMH that can occur in the absence of observable sensitising events. This is known as routine antenatal anti-D prophylaxis (RAADP). The use of anti-D immunoglobulin for RAADP is in addition to the administration of anti-D immunoglobulin following potentially sensitising events, and its use in either indication is not affected by prior use in the other.
- 2.5 The incidence of HDN depends on the proportion of the population that is RhD negative. This proportion varies between ethnic groups and is highest in the white population; in the UK, approximately 16% of the white population is RhD negative. For 2005, it was estimated that approximately 65,000 RhD-positive babies were born in the UK to women who were RhD negative (10% of all births). Without RAADP, but with the use of anti-D immunoglobulin after sensitising events, 1% of these

women (approximately 650) would have become sensitised. Of these, approximately 550 would go on to have a further pregnancy. Taking into account subsequent pregnancies, it is estimated that about 520 affected pregnancies in England and Wales per year would require close monitoring because the mother is RhD negative and has been sensitised. Between 10% and 12% of these babies would require intrauterine transfusions. It is estimated that fetal anaemia and HDN would lead to approximately 37 fetal or neonatal deaths, 21 children with minor developmental problems and eight children with major developmental problems.

- 2.6 RAADP can be given as two doses of anti-D immunoglobulin of 500 IU (one at 28 weeks and one at 34 weeks gestation), as two doses of anti-D immunoglobulin of 1000–1650 IU (one at 28 weeks and one at 34 weeks gestation), or as a single dose of 1500 IU either at 28 weeks or between 28 and 30 weeks gestation. RAADP is not used uniformly throughout the NHS. In 2005, a survey of obstetric units reported that 75% offered RAADP, and of these 81% used one of the two-dose regimens. RAADP is usually administered by community midwives or at antenatal clinics.

### 3 The technologies

- 3.1 D-Gam (Bio Products Laboratory) is extracted by fractionation and is suitable for intramuscular use only. It is sold as a solution ready for injection, and is available in vials containing 250, 500, 1500 or 2500 IU. The 500 IU dose has UK marketing authorisation for RAADP at 28 and 34 weeks gestation in non-sensitised women who are RhD negative, for use after potentially sensitising events that occur after 20 weeks gestation, and for use after the birth of an RhD-positive baby. The 250 IU dose has UK marketing authorisation for use after potentially sensitising events up to 20 weeks gestation, and the 1500 and 2500 IU doses have UK marketing authorisation for the treatment of large FMHs. D-Gam also has UK marketing authorisation for the treatment of people who are RhD negative and who have had transfusions of RhD-positive blood or blood products.
- 3.2 Partobulin SDF (Baxter BioScience) is prepared by a modified fractionation process and is suitable for intramuscular use only. It is available in prefilled syringes containing 1250 IU. For RAADP, it has UK marketing authorisation for two intramuscular doses of 1000–1650 IU given at 28 and 34 weeks gestation. It also has UK marketing authorisation for use post partum, for use after potentially sensitising events, and for the treatment of people who are RhD negative and who have had transfusions of RhD-positive blood or blood products.
- 3.3 Rhophylac (CSL Behring) is extracted by cation-exchange column chromatography and may be given intramuscularly or intravenously. It is available in prefilled syringes containing 1500 IU. It has UK marketing authorisation for RAADP as a single dose of 1500 IU given between 28 and 30 weeks gestation. It also has UK marketing authorisation for use post partum, for use after potentially sensitising events, and for the treatment of people who are RhD negative and who have had transfusions of RhD-positive blood or blood products.
- 3.4 WinRho SDF (Baxter BioScience) is extracted by anion-exchange column chromatography and may be given intravenously or intramuscularly. It is available as a powder for reconstitution. It has UK marketing



authorisation for RAADP at a single dose of 1500 IU to be given at 28 weeks gestation. It also has UK marketing authorisation for use post partum, for use after potentially sensitising events, and for the treatment of people who are RhD negative and who have had transfusions of RhD-positive blood or blood products. In the UK, it is currently marketed solely for the treatment of idiopathic thrombocytopenic purpura.

- 3.5 All preparations of anti-D immunoglobulin carry a small risk of localised or generalised allergic reactions. Anti-D immunoglobulin is extracted from donor blood and, although blood donors are carefully screened for transmissible infections, there is always a small risk of the transmission of blood-borne infections. For full details of side effects and contraindications, see the summary of product characteristics for each technology.
- 3.6 D-Gam costs £27 per 500-IU vial (£54 per two-dose course). Partobulin SDF costs £35 per 1250-IU prefilled syringe (£70 per two-dose course). Rhophylac costs £46.50 per 1500-IU prefilled syringe. WinRho SDF costs £313.50 per 1500-IU vial. All costs exclude VAT and are from the 'British national formulary' (edition 53). Costs may vary in different settings because of negotiated procurement discounts.

## 4 Evidence and interpretation

The Appraisal Committee ([appendix A](#)) considered evidence from a number of sources ([appendix B](#)).

### 4.1 Clinical effectiveness

4.1.1 The Assessment Group identified eight trials from the previous appraisal 'Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women' (NICE technology appraisal guidance 41) that compared a group receiving RAADP using one of the currently licensed regimens with a control group, and that were suitable for inclusion in the current review. Four trials used a dose of 500 IU at both 28 and 34 weeks gestation, one trial used a dose of 1500 IU at both 28 and 34 weeks gestation, and three trials used a single dose of 1500 IU at 28 weeks gestation. Five new publications were identified by the Assessment Group: one of these presented follow-up data from a trial included in the original review, relating to women during subsequent pregnancies; a further three related to two trials included in the original review but did not present new data; and one was a new randomised controlled trial (RCT) comparing intravenous with intramuscular Rhophylac. This new RCT was included in the current review, along with the eight studies from the previous appraisal.

4.1.2 Only one study was an RCT (the new study that compared intramuscular and intravenous Rhophylac), but this was not powered to detect differences between the two treatment arms. One study was a quasi-RCT with year of birth used to allocate participants to treatment groups. One of the other studies was a community intervention trial (controlled before-and-after study), one was a retrospective before-and-after trial, and five were non-randomised studies with historical or geographical controls. Studies that use historical controls may overestimate the effectiveness of RAADP because changes in obstetric care may have led to a decrease in sensitisation. Alternatively, the use of historical controls may underestimate the effectiveness of RAADP because newer assays for maternal anti-D antibody are more sensitive. The use of geographical

controls may be confounded by variations in obstetric practice.

- 4.1.3 Five studies recruited only primigravidae (women with a first pregnancy) and four recruited primigravidae and non-sensitised multigravidae (women with a second or subsequent pregnancy). Most studies reported the rate of sensitisation according to the presence of maternal anti-D antibody at the time of delivery and 6 months after delivery. However, the true rate of sensitisation is higher because of the phenomenon of silent sensitisation. Silent sensitisation means that women have no detectable anti-D antibody, but have developed the template for antibody production and will mount an augmented immune response after FMH in any future pregnancy with an RhD-positive baby. Four studies done in primigravidae reported sensitisation rates in subsequent pregnancies, and one of these provided data on the incidence of sensitisation in subsequent pregnancies in which RAADP was not given. Only two studies took as their primary endpoint the number of women who were RhD negative, who had a baby that was RhD positive and who were found to be sensitised during a subsequent pregnancy with an RhD-positive fetus.
- 4.1.4 The results across the control groups (women who did not receive RAADP but may have received anti-D immunoglobulin for other indications) were broadly similar; the proportion sensitised ranged from 1.2% to 1.8% (0.8–1.6% in primigravidae and 1.4–2.2% in multigravidae). Over time there was a reduction in the number of women in the control group found to be sensitised during a subsequent pregnancy with an RhD-positive fetus. This could have been a result of improved obstetric practice as well as an improved uptake of anti-D immunoglobulin for potentially sensitising events. In all studies, the rate of sensitisation was lower in the intervention (RAADP) arm. Because the new RCT identified was not sufficiently similar to the previous studies to allow its inclusion in a meta-analysis, the results of the meta-analysis from the original review were considered valid.
- 4.1.5 This meta-analysis divided the trials into three groups: group 1 comprised four studies that used a dose of 500 IU at both 28 and 34 weeks gestation in primigravidae; group 2 comprised three studies that used a dose of 1500 IU at 28 weeks gestation and included

primigravidae and multigravidae; and group 3 comprised two community-based trials in the UK that used a dose of 500 IU at both 28 and 34 weeks gestation in primigravidae. Group 3 was considered the most representative for the cost-effectiveness analysis. This group consisted of UK-based community trials that took as their primary endpoint the number of women who were RhD negative, who had a baby that was RhD positive and who were found to be sensitised in a subsequent pregnancy with an RhD-positive fetus. These trials used an intention-to-treat analysis of all women within a geographical area and demonstrated the likely reduction in sensitisation rate achievable in practice. The sensitisation rate from the meta-analysis of these two trials was 0.95% in the control group (95% confidence interval [CI] 0.18 to 1.71%) and 0.35% in the treatment group (95% CI 0.29 to 0.40%). This represents an absolute reduction in risk of sensitisation in women who are RhD negative and at risk (that is, carrying an RhD-positive baby) of 0.6%, with an odds ratio of sensitisation for RAADP of 0.37 (95% CI 0.21 to 0.65).

- 4.1.6 There were no trials comparing the two-dose regimen (doses given at 28 and 34 weeks) with a single dose given between 28 and 30 weeks, and no evidence of a difference in efficacy between these regimens.

## 4.2 Cost effectiveness

- 4.2.1 A systematic review of the cost effectiveness of RAADP identified 11 papers relating to nine studies. Five studies used UK costs, but only two evaluations were applicable to the NHS. One study calculated incremental costs per case of HDN and fetal loss prevented. The results suggested that for most anti-D regimens the use of RAADP in primigravidae would be cost saving in terms of prevention of sensitisation and fetal loss. When RAADP for all women who are RhD negative was compared with RAADP for primigravidae who are RhD negative, the additional cost per incident of sensitisation prevented ranged from £2900 to £8300 depending on the regimen used. The cost per HDN-associated fetal loss avoided was between £42,000 and £120,000. Another study suggested that a programme of RAADP would be cost saving if HDN was eradicated. Similar cost savings were predicted in a study of RAADP in England and Wales. The independent economic evaluation for the previous appraisal (NICE technology

appraisal guidance 41) calculated that the incremental cost-effectiveness ratio (ICER) for RAADP was £11,000–13,000 per quality-adjusted life year (QALY) gained for primigravidae compared with no prophylaxis. For multigravidae compared with primigravidae, the ICER was £46,000–52,000 per QALY gained. The evaluation also suggested that adding a utility gain for avoiding fetal loss and interventions in the next pregnancy could reduce the ICER for multigravidae.

4.2.2 No economic models were submitted from the manufacturers.

4.2.3 The Assessment Group modelled a cohort of RhD-negative primigravidae and multigravidae. It assumed the UK birth rate to be 12.1 per 1000 women and that 16% of the population is RhD negative. Each regimen for RAADP was compared with no RAADP. It was assumed that women in their second and subsequent pregnancies had received RAADP in their first pregnancy. The base-case sensitisation rate was assumed to be 0.95% and the odds ratio for each of the regimens of RAADP was assumed to be 0.37. It was assumed that in their first pregnancy 61% of women who are RhD negative will have an RhD-positive fetus and are therefore at risk. This figure was calculated based on the fact that 84% of men are RhD positive, of whom 55% are heterozygous and have a 50% chance of fathering a baby who is RhD positive. Of the 61% of RhD-negative women who are at risk, 0.35% will be sensitised during their first pregnancy. A certain proportion of these (85%) are then expected to go on to have a second baby. Approximately 70% of these babies will be RhD positive because a mother who has had one RhD-positive child is more likely to have another. These babies are at risk of developing HDN. A further 0.35% of women who are not sensitised during their first pregnancy will be sensitised during their second. A smaller proportion (40%) of these either go on to have a third pregnancy where the baby may be at risk of HDN as a result of sensitisation in the first or second pregnancy, or are at risk of sensitisation during their third pregnancy. Similarly, 35% of women who have had three pregnancies go on to have a fourth pregnancy.

4.2.4 The Assessment Group assumed that the probability of fetal loss in pregnancies of sensitised women is around 4%, and that 6% of babies with HDN will have minor developmental problems. Within the model, a

child with minor developmental problems had a health utility score of 0.85 and was assumed to incur a cost of £100 per year until 16 years of age. The Assessment Group assumed that 3% of babies with HDN would have major developmental problems. For these children, a health utility score of 0.42 and a cost of £458 per year, over a life expectancy of 60 years, were assumed. The costs of the preparations of anti-D immunoglobulin were taken from the 'British national formulary' (edition 53). Each anti-D injection was assumed to incur an administration cost of £5. The cost of managing a pregnancy in a sensitised mother was estimated to be £2885.

- 4.2.5 The model assumed that the first RhD-positive child born to an RhD-negative mother is unaffected, and that the risk of sensitisation and the effectiveness of RAADP remain the same in successive pregnancies. In the base case, the model assumes that the loss of a fetus or neonate because of HDN is associated with a 10-QALY loss, in keeping with the previous appraisal (NICE technology appraisal guidance 41).
- 4.2.6 In the base-case analysis for primigravidae who are RhD negative, comparison of RAADP with no prophylaxis resulted in ICERs of £14,802 (Rhophylac), £19,438 (D-Gam), £25,372 (Partobulin SDF) and £113,827 (WinRho SDF) per QALY gained. For all women who are RhD negative (multigravidae and primigravidae) compared with RhD-negative primigravidae, the ICERs for RAADP were £34,336 (Rhophylac), £45,172 (D-Gam), £59,043 (Partobulin SDF) and £265,807 (WinRho SDF) per QALY gained.
- 4.2.7 One-way sensitivity analyses suggested that the model results were sensitive to the base-case sensitisation rate and the odds ratio for the sensitisation rate associated with RAADP. The number of QALYs lost because of fetal loss, the rate of fetal loss owing to HDN and the rate of major disability owing to HDN also had significant impacts on the ICER.
- 4.2.8 The Assessment Group conducted additional analyses that combined primigravidae and multigravidae into one group. Treating the combined group with RAADP was compared with giving no RAADP. This comparison resulted in ICERs of £21,156 for Rhophylac, £27,810 for D-Gam, £36,326 for Partobulin SDF and £163,268 for WinRho SDF per

QALY gained.

## 4.3 Consideration of the evidence

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of RAADP for women who are RhD negative, having considered evidence on the nature of the condition and the value placed on the benefits of RAADP by pregnant women who are RhD negative, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 The Committee considered the evidence on the clinical effectiveness of RAADP. The Committee acknowledged that the clinical trials showed that the use of RAADP reduced the rate of sensitisation in primigravidae and multigravidae who are RhD negative. The Committee heard testimony from the clinical specialists that RAADP is considered to be an effective intervention, although it is not possible to determine what proportion of the total benefit of the use of anti-D immunoglobulin treatment (including use as prophylaxis after potentially sensitising events) is derived from RAADP. The Committee was aware that treatment with RAADP carries the usual risks associated with blood products. However, it heard from the clinical specialists and patient experts that the benefits of using RAADP are much greater than the risks, and that the use of anti-D immunoglobulin, including routine prophylaxis, provides reassurance for pregnant women who are RhD negative. The Committee recognised that anti-D immunoglobulin has no clinical benefit for women who have been previously sensitised. The Committee concluded that RAADP is clinically effective in reducing sensitisation and therefore in reducing the risk of HDN and its consequences.
- 4.3.3 The Committee considered the costs included in the economic model. The Committee noted that the costs of managing a severe disability were derived from a study of young adults with hemiplegic cerebral palsy and were limited to NHS costs for inpatient, outpatient and emergency care as well as primary care and healthcare in the community. The Committee heard from the clinical specialists that children with a severe disability resulting from HDN were likely to require more NHS resources and a greater range of services than those provided to the young adults in the

study. The Committee also heard from the clinical specialists that the cost of managing a pregnancy in a sensitised woman was likely to have been underestimated in the economic model. The Committee concluded that the actual costs to the NHS and to personal social services both of managing a severe disability and of managing a sensitised pregnancy were likely to be much greater than those included in the economic model.

- 4.3.4 The Committee considered the value that the economic model attached to the loss of a fetus or neonate owing to HDN. The Committee recognised that it was difficult to ascribe a precise utility value to this aspect of the use of the technology, and noted that during the original appraisal (NICE technology appraisal guidance 41) the loss of a fetus late in pregnancy or at birth was assumed to be equivalent to a loss of at least 10 QALYs. The Committee concluded that, in the absence of other data, a disutility for fetal loss of 10 QALYs should also be applied in this appraisal. The Committee noted that parents also experience disutility as a result of the intensive intervention necessary in subsequent pregnancies if sensitisation has occurred, as well as in caring for a child with disability owing to HDN.
- 4.3.5 The Committee considered the evidence that treatment with RAADP is most cost effective in the first pregnancy and becomes less cost effective with each subsequent pregnancy. The Committee was aware of the need to consider subgroups with differential cost effectiveness and that multigravidae could be further subdivided according to parity and therefore the cost-effectiveness of RAADP. The Committee considered that separate consideration of each pregnancy would cause practical difficulties in refusing women an effective intervention that they had received in an earlier pregnancy. The Committee therefore concluded that it would be more appropriate to consider the cost effectiveness of offering RAADP to all pregnant women who are RhD negative.
- 4.3.6 The Committee considered the results of the cost-effectiveness analysis. The cost-effectiveness analysis for three of the products resulted in ICERs of between £21,000 and £36,000 per QALY gained for giving RAADP to all women who are RhD negative, irrespective of the number of previous pregnancies, compared with not using RAADP. The Committee



acknowledged that the costs associated with the management of a pregnancy in a sensitised woman and with caring for a child with severe disability had been underestimated in the model, and that the disutility of caring for a child with disability was not included in the model. The use of more realistic values for these parameters in the model would decrease the ICERs. The Committee concluded that RAADP is therefore a cost-effective use of NHS resources. The Committee noted that the product WinRho SDF, although licensed, is not marketed for RAADP; in addition, the ICERs for this product would be unacceptably high and it could not therefore be considered as cost effective.

4.3.7 The Committee acknowledged that it is also standard practice to give anti-D immunoglobulin within 72 hours to all women who are RhD negative who give birth to RhD-positive babies, and after potentially sensitising events to all women who are RhD negative. RAADP is given in addition to the anti-D treatment given in these situations. Moreover, use of RAADP is not affected by the administration of anti-D immunoglobulin for other indications earlier in the pregnancy.

4.3.8 The Committee considered the use of single-dose and two-dose regimens. The Committee was aware that there was no evidence of a difference in effectiveness between the regimens. The Committee acknowledged that the differences in cost effectiveness were solely a result of the differences in price of the products, and that the two-dose regimen was associated with higher administration costs than used in the economic model because the second dose may require an extra clinic visit. The Committee noted that use of a single-dose regimen may improve compliance by avoiding logistical failures associated with a second dose, but this would have no effect if the reason for non-compliance is a woman's refusal of treatment. The clinical specialists informed the Committee that, depending on local practice, it may not be possible to administer either the single-dose or the two-dose regimen at routinely scheduled antenatal visits. This may necessitate setting up additional clinics specifically to administer anti-D immunoglobulin, which would incur additional costs. The Committee also heard theoretical concerns that a single-dose regimen may not provide protection towards the end of pregnancy. In addition, the Committee was aware that consideration should be given to limiting a woman's exposure to different

batches of anti-D immunoglobulin. Finally, the Committee heard that there are occasionally supply problems with individual products, and that the option of having a range of suppliers was important to ensure the continued availability of anti-D treatment. In summary, the Committee decided that it could not make a firm recommendation for either the single-dose or the two-dose regimen. The Committee also concluded that, although it was not possible to recommend a particular product, individual purchasers should use the product with the lowest cost available locally, taking into account the acquisition cost as well as the costs associated with administration.

- 4.3.9 The Committee was aware that there maybe circumstances in which a woman cannot receive treatment with anti-D immunoglobulin because of strongly held beliefs that make it impossible for her to accept treatment with blood products. The Committee recognised that passive immunisation is not possible for such women, and that no alternative treatment options exist. The Committee also acknowledged that in certain circumstances it may be unnecessary for a woman who is RhD negative to receive RAADP; for example, if she is planning to have no more children or is in a stable relationship with a man known to be RhD negative. The Committee concluded that a woman eligible for RAADP should be given the opportunity to discuss the benefits and risks so that she can make an informed choice about the use of the treatment.

## 5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient is rhesus D negative and the doctor responsible for their care thinks that routine antenatal anti-D prophylaxis is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.4 NICE has developed tools to help organisations implement this guidance (listed below).
- A costing statement explaining the resource impact of this guidance.
  - Audit support for monitoring local practice.

## 6 Recommendations for further research

- 6.1 The Committee was aware that a test is currently being developed that determines fetal blood type by genotyping of fetal DNA present in the maternal circulation.
- 6.2 Head-to-head trials of single-dose versus two-dose RAADP regimens are required to establish relative efficacy.
- 6.3 A study to better estimate the disutility of fetal and neonatal loss, as well as the disutility to parents who experience such a loss, is required.

## 7 Related NICE guidance

Antenatal care: routine care for the healthy pregnant woman. NICE clinical guideline 62 (2008).

## 8 Review of guidance

- 8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 8.2 The guidance on this technology was considered for review in August 2011. Details are available on the [NICE website](#).

Andrew Dillon  
Chief Executive  
August 2008

# Appendix A: Appraisal Committee members, guideline representatives and NICE project team

## A Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the [NICE website](#).

### **ProfessorDavidBarnett**

Professor of Clinical Pharmacology, University of Leicester

### **DrBrianBuckley**

Chairman, Incontact

### **DrCarolCampbell**

Senior Lecturer, University of Teesside

### **ProfessorMikeCampbell**

Professor of Medical Statistics, University of Sheffield

### **ProfessorDavidChadwick**

Professor of Neurology, University of Liverpool

**DrChristineDavey**

Senior Researcher, North Yorkshire Alliance Research and Development Unit

**DrMikeDavies**

Consultant Physician, Manchester Royal Infirmary

**MrRichardDevereaux-Phillips**

Public Affairs Manager, Medtronic

**ProfessorRachelAElliott**

Lord Trent Professor of Medicines and Health, University of Nottingham

**MrsEleanorGrey**

Lay member

**DrDyfrigHughes**

Senior Research Fellow in Pharmacoeconomics, Centre for the Economics of Health and Policy in Health, University of Wales

**DrCatherineJackson**

Clinical Lecturer in Primary Care Medicine, Alyth Health Centre

**DrPeterJackson**

Clinical Pharmacologist, Sheffield Teaching Hospitals NHS Foundation Trust

**ProfessorPeterJones**

Professor of Statistics and Pro Vice Chancellor for Research and Enterprise, Keele University

**MsRachelLewis**

Practice Development Facilitator, Manchester Primary Care Trust

**DamienLongson**

Consultant in Liaison Psychiatry, North Manchester General Hospital

**ProfessorJonathanMichaels**



Professor of Vascular Surgery, University of Sheffield

**DrEugeneMilne**

Deputy Medical Director, North East Strategic Health Authority

**DrSimonMitchell**

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

**DrRichardAlexanderNakielny**

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

**DrMartinJPrice**

Head of Outcomes Research, Janssen-Cilag

**DrPhilipRutledge**

GP and Consultant in Medicines Management, NHS Lothian

**MrMilesScott**

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

**ProfessorAndrewStevens**

Chair of Appraisal Committee C

**DrCathrynThomas**

GP and Associate Professor, University of Birmingham

**MrWilliamTurner**

Consultant Urologist, Addenbrooke's Hospital, Cambridge

## **B Guideline representatives**

The following individual, representing the Guideline Development Group responsible for developing the Institute's clinical guideline related to this topic, was invited to attend the ACD meeting to observe and to contribute as an adviser to the Committee.

- Sue Latchem, Guidelines Commissioning Manager, NICE

## C NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**ElangovanGajraj**

Technical Lead

**JoannaRichardson**

Technical Adviser

**ChrisFeinmann**

Project Manager

## Appendix B: Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by the University of Sheffield, School of Health and Related Research (SchHARR)

- Pilgrim H, Lloyd-Jones M, Rees A. Routine antenatal anti-D prophylaxis for RhD-negative women (review), November 2007.

B. The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I) Manufacturers/sponsors:

- Baxter BioScience (Partobulin SDF, WinRho SDF)
- Bio Products Laboratory (D-Gam)
- CSL Behring (Rhophylac)

II) Professional/specialist and patient/carers groups:

- The Miscarriage Association
- The National Childbirth Trust (NCT)
- Association of Radical Midwives
- NHS Blood and Transplant
- Royal College of General Practitioners
- Royal College of Midwives
- Royal College of Nursing
- Royal College of Obstetricians and Gynaecologists

- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Physicians

III) Other organisations:

- Bexley Care Trust PCT
- Department of Health
- Nottingham City PCT
- Welsh Assembly Government

IV) Commentator organisations (without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- School of Health and Related Research, University of Sheffield
- National Coordinating Centre for Health Technology Assessment

C. The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on RAADP for women who are RhD negative by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Ann Benton, Consultant Haematologist, nominated by the Royal Colleges of Pathologists and Physicians – clinical specialist
- Dr Alan Cameron, Consultant Obstetrician, nominated by NHS Quality Improvement Scotland (QIS) – clinical specialist
- Mrs Emma Wightman, Osteopath and NCT Antenatal Teacher Trainee, nominated by the NCT – patient expert

## Changes after publication

**February 2014:** implementation section updated to clarify that routine antenatal anti-D prophylaxis is recommended as an option for treating women who are rhesus D negative. Additional minor maintenance update also carried out.

**March 2012:** minor maintenance

## About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [multiple technology appraisal](#) process.

It replaces 'The clinical effectiveness and cost effectiveness of routine anti-D prophylaxis for RhD-negative women in pregnancy' (NICE technology appraisal guidance 41) issued in May 2002.

The Institute reviews each piece of guidance it issues. This review and re-appraisal of routine antenatal anti-D prophylaxis (RAADP) for women who are rhesus D (RhD) negative has resulted in no change to the recommendations regarding which women are eligible for RAADP and the indications for its use. This review has appraised preparations that can be administered as single-dose or two-dose regimens, and recommends that the preparation with the lowest associated cost should be used.

The recommendations from this guideline have been incorporated into a [NICE Pathway](#). We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

### Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with

those duties.

## Copyright

© National Institute for Health and Clinical Excellence 2008. All rights reserved. NICE copyright material can be downloaded for private research and study, and may be reproduced for educational and not-for-profit purposes. No reproduction by or for commercial organisations, or for commercial purposes, is allowed without the written permission of NICE.

## Accreditation

